Sandoz—Cont.

FIORICET®

[fē-ōr'i-set]

(Butalbital, Acetaminophen, and Caffeine Tablets, USP)

Caution: Federal law prohibits dispensing without prescription.

The following prescribing information is based on official labeling in effect on August 1, 1996.

DESCRIPTION

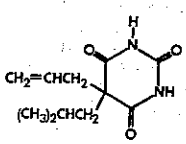
Fioricet® (Butalbital, Acetaminophen, and Caffeine Tablets, USP) is supplied in tablet form for oral administration. Each tablet contains:

butalbital*, USP	50 mg
*Warning: May be habit-forming.	
acetaminophen, USP	325 mg
caffeine, USP	40 mg

Active Ingredients: butalbital, USP, acetaminophen, USP, and caffeine, USP.

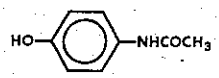
Inactive Ingredients: crospovidone, FD&C Blue #1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid.

Butalbital (5-allyl-5-isobutylbarbituric acid), is a short to intermediate-acting barbiturate. It has the following structural formula:



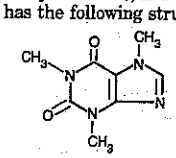
$C_{11}H_{16}N_2O_3$ Mol. wt. 224.26

Acetaminophen (4'-hydroxyacetanilide), is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ Mol. wt. 151.16

Caffeine (1,3,7-trimethylxanthine), is a central nervous system stimulant. It has the following structural formula:



$C_8H_{10}N_4O_2$ Mol. wt. 194.19

CLINICAL PHARMACOLOGY

This combination drug product is intended as a treatment for tension headache.

It consists of a fixed combination of butalbital, acetaminophen and caffeine. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

Pharmacokinetics

The behavior of the individual components is described below.

Butalbital

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59% to 88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2, 3-dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% is conjugated.

See *OVERDOSAGE* for toxicity information.

Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See *OVERDOSAGE* for toxicity information.

Caffeine

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methylxanthine and 1-methyluric acid. Of the 70% of the dose that is recovered in the urine, only 3% is unchanged drug.

See *OVERDOSAGE* for toxicity information.

INDICATIONS AND USAGE

Fioricet® (Butalbital, Acetaminophen, and Caffeine Tablets) is indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

CONTRAINDICATIONS

This product is contraindicated under the following conditions:

—Hypersensitivity or intolerance to any component of this product

—Patients with porphyria.

WARNINGS

Butalbital is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS

General

Butalbital, acetaminophen and caffeine tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment or renal or hepatic function, or acute abdominal conditions.

Information for Patients

This product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

Butalbital, acetaminophen and caffeine may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether acetaminophen or butalbital have a potential for carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C: Animal reproduction studies have not been conducted with this combination product. It is also not known whether butalbital, acetaminophen and caffeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This product should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last two months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Nursing Mothers

Caffeine, barbiturates and acetaminophen are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from butalbital, acetaminophen and caffeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Frequently Observed

The most frequently reported adverse reactions are dizziness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxication feeling.

Infrequently Observed

All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling sensation, fainting, fatigue, heavy eyelids, high energy, hot flashes, numbness, sluggishness, seizure. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported.

The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in the *OVERDOSAGE* section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

DRUG ABUSE AND DEPENDENCE

Abuse and Dependence

Butalbital

Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerance by the patient.

OVERDOSAGE

Following an acute overdosage of butalbital, acetaminophen and caffeine, toxicity may result from the barbiturate or the acetaminophen. Toxicity due to caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms

Toxicity from ***barbiturate*** poisoning include drowsiness, confusion, and coma; respiratory depression; hypotension and hypovolemic shock.

In ***acetaminophen*** overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necroses, hypoglycemic coma and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, but fatalities with less than 15 grams.

Acute ***caffeine*** poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia and extrasystole.

Treatment

A single or multiple overdose with this combination product is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an

...cathartic. If repeated doses are used, the cathartic ...included with alternate doses as required. Hypoten... usually hypovolemic and should respond to fluids. ...should be avoided. A cuffed endotracheal tube ...be inserted before gastric lavage of the unconscious ...and, when necessary, to provide assisted respiration. ...function is normal, forced diuresis may aid in the ...of the barbiturate. Alkalinization of the urine ...renal excretion of some barbiturates, especially ...barbital.

...attention should be given to maintaining ade... ...pulmonary ventilation. In severe cases of intoxication, ...dialysis,. or preferably hemodialysis may be ...If hypoprothrombinemia occurs due to aceta... ...overdose, vitamin K should be administered ...parenterally.

...of acetaminophen may have exceeded 140 mg/kg, ...gastric lavage should be administered as early as possible. ...acetaminophen levels should be obtained, since levels ...four hours following ingestion help predict aceta... ...toxicity. Do not await acetaminophen assay re... ...before initiating treatment. Hepatic enzymes should be ...and initially, and repeated at 24-hour intervals. ...methemoglobinemia over 30% should be treated with meth... ...blue by slow intravenous administration.

...Doses (for adults)

...barbital:	toxic dose 1.0 g	(20 tablets)
...acetaminophen:	toxic dose 10.0 g	(30 tablets)
...caine:	toxic dose 1.0 g	(25 tablets)

...AGE AND ADMINISTRATION

...1 or 2 tablets every 4 hours as needed. Total daily dosage ...not exceed 6 tablets.

...ged and repeated use of this product is not recom... ...because of the potential for physical dependence.

...HOW SUPPLIED

...cet® ...barbital, Acetaminophen, and Caffeine Tablets, USP)

...containing 50 mg butalbital, 325 mg acetaminophen, and ...mg caffeine. Available as light-blue, round compressed ...tablets, engraved "FIORICET" and "℞" on one side, ...bead profile "(( ))" on other side. Bottles of 100 (NDC ...0084-05) and 500 (NDC 0078-0084-08).

...Pak® (unit-dose) packages of 100, 10 blister strips of ...(NDC 0078-0084-06).

...and Dispense

...below 86°F (30°C); dispense in a tight container. ...[REV: MARCH 1996 30131903]

...tions in *Product Identification Guide, page 332*

...cet® with CODEINE

...barbital, acetaminophen, caffeine, and ...phosphate)

...Rx Only

...Federal law prohibits dispensing without pre...

...following prescribing information is based on official ...in effect on August 1, 1996.

...SCRIPTION

...® with Codeine (butalbital, acetaminophen, caf... ...and codeine phosphate) is supplied in capsule form for ...administration.

...capsule contains:

...phosphate, USP	30 mg (1/2 gr)
...Warning: May be habit-forming.	
...barbital, USP	50 mg
...Warning: May be habit-forming.	
...caffeine, USP	40 mg
...acetaminophen, USP	325 mg

...phosphate [morphine-3-methyl ether phosphate ...(salt) hemihydrate, $C_{18}H_{24}NO_7P$, anhydrous ...37), a white crystalline powder, is a narcotic analge... ...antitussive.

...barbital (5-allyl-5-isobutylbarbituric acid, $C_{11}H_{16}N_2O_3$, ...180), a slightly bitter, white crystalline powder, is a ...to intermediate-acting barbiturate.

...caine (1,3,7-trimethylxanthine, $C_8H_{10}N_4O_2$, mw 194.19), a ...white crystalline powder, is a central nervous system ...ant.

...acetaminophen (4'-hydroxyacetanilide, $C_8H_9NO_2$, ...151.16), a slightly bitter white crystalline powder, is a ...non-salicylate analgesic and antipyretic.

...Ingredients: codeine phosphate, USP, butalbital, ...caffeine, USP, and acetaminophen, USP.

...Ingredients: black iron oxide, colloidal silicon diox... ...D&C Red #7 (calcium lake), D&C Red #33, FD&C Blue ...D&C Blue #1 (aluminum lake), gelatin, magnesium ...pregelatinized starch, red iron oxide, sodium lauryl ...and titanium dioxide.

May also include: benzyl alcohol, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

CLINICAL PHARMACOLOGY

Fioricet® with Codeine is a combination drug product intended as a treatment for tension headache.

Fioricet® consists of a fixed combination of butalbital 50 mg, acetaminophen 325 mg and caffeine 40 mg. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

Pharmacokinetics

The behavior of the individual components is described below.

Codeine

Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

See *OVERDOSAGE* for toxicity information.

Butalbital

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59%–88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% is conjugated.

See *OVERDOSAGE* for toxicity information.

Caffeine

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that is recovered in the urine, only 3% is unchanged drug.

See *OVERDOSAGE* for toxicity information.

Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25–3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See *OVERDOSAGE* for toxicity information.

INDICATIONS

Fioricet® with Codeine is indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of Fioricet® with Codeine in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusable.

CONTRAINDICATIONS

Fioricet® with Codeine is contraindicated under the following conditions:

—Hypersensitivity or intolerance to acetaminophen, caffeine, butalbital, or codeine.

—Patients with porphyria.

WARNINGS

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fioricet® with Codeine is not recommended.

PRECAUTIONS

General

Fioricet® with Codeine should be prescribed with caution in certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

Information for Patients

Fioricet® with Codeine may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fioricet® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with Fioricet® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

Fioricet® with Codeine may enhance the effects of:

—Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions

Codeine

Codeine may increase serum amylase levels.

Acetaminophen

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether acetaminophen, codeine and butalbital have a potential for carcinogenesis or mutagenesis. No adequate studies have been conducted in animals to determine whether acetaminophen and butalbital have a potential for impairment of fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C: Animal reproduction studies have not been conducted with Fioricet® with Codeine. It is also not known whether Fioricet® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fioricet® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Labor and Delivery

Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers

Caffeine, barbiturates, acetaminophen and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

Continued on next page